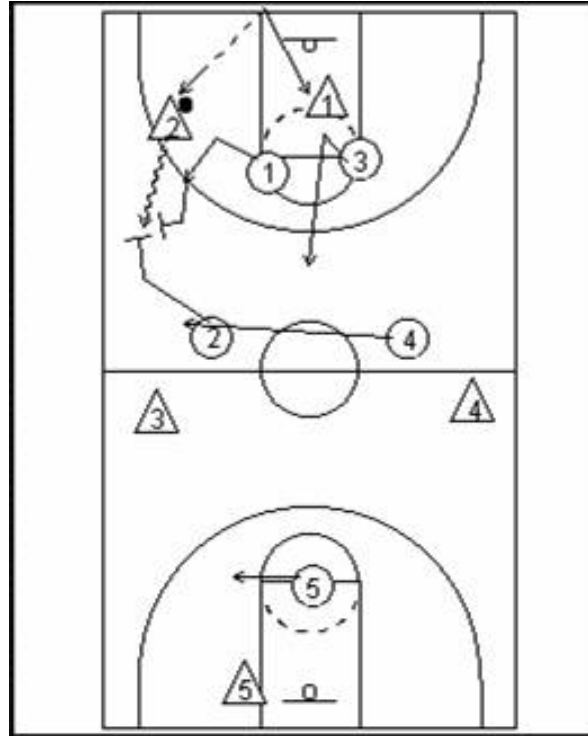
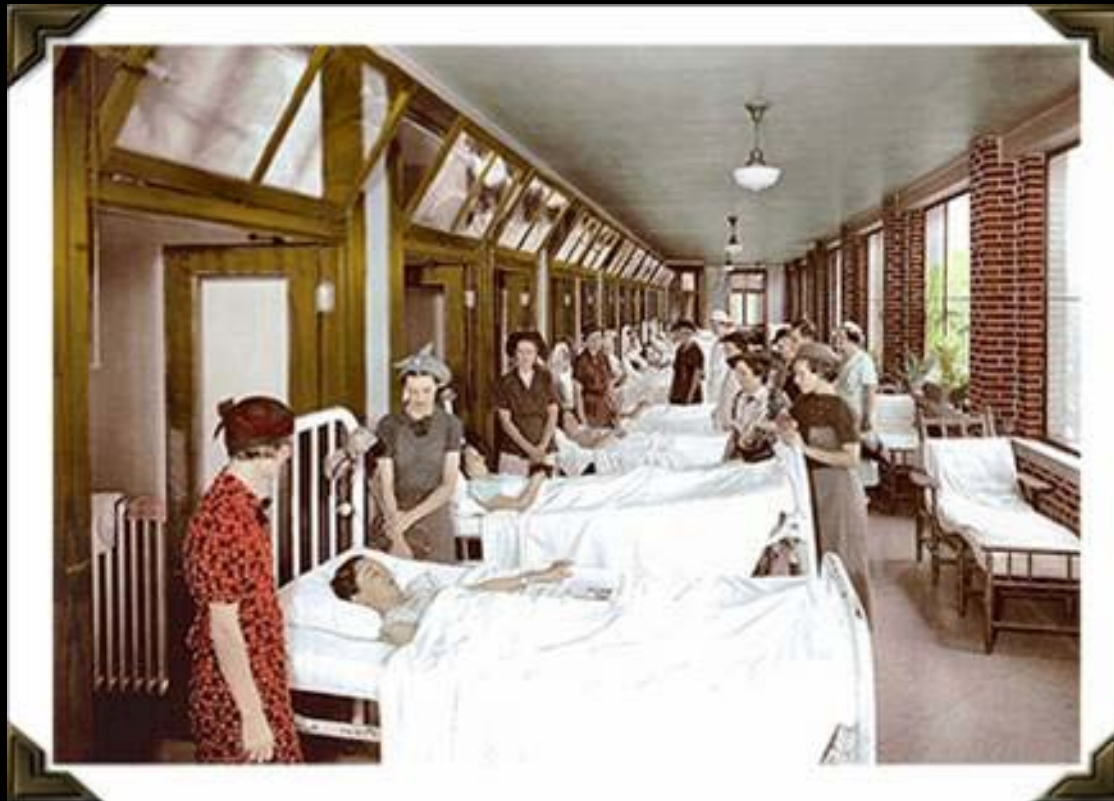


# ***Tuberculosis: Pressing On***



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**Massachusetts Department of Public Health**



## Outline

US/MA Trends

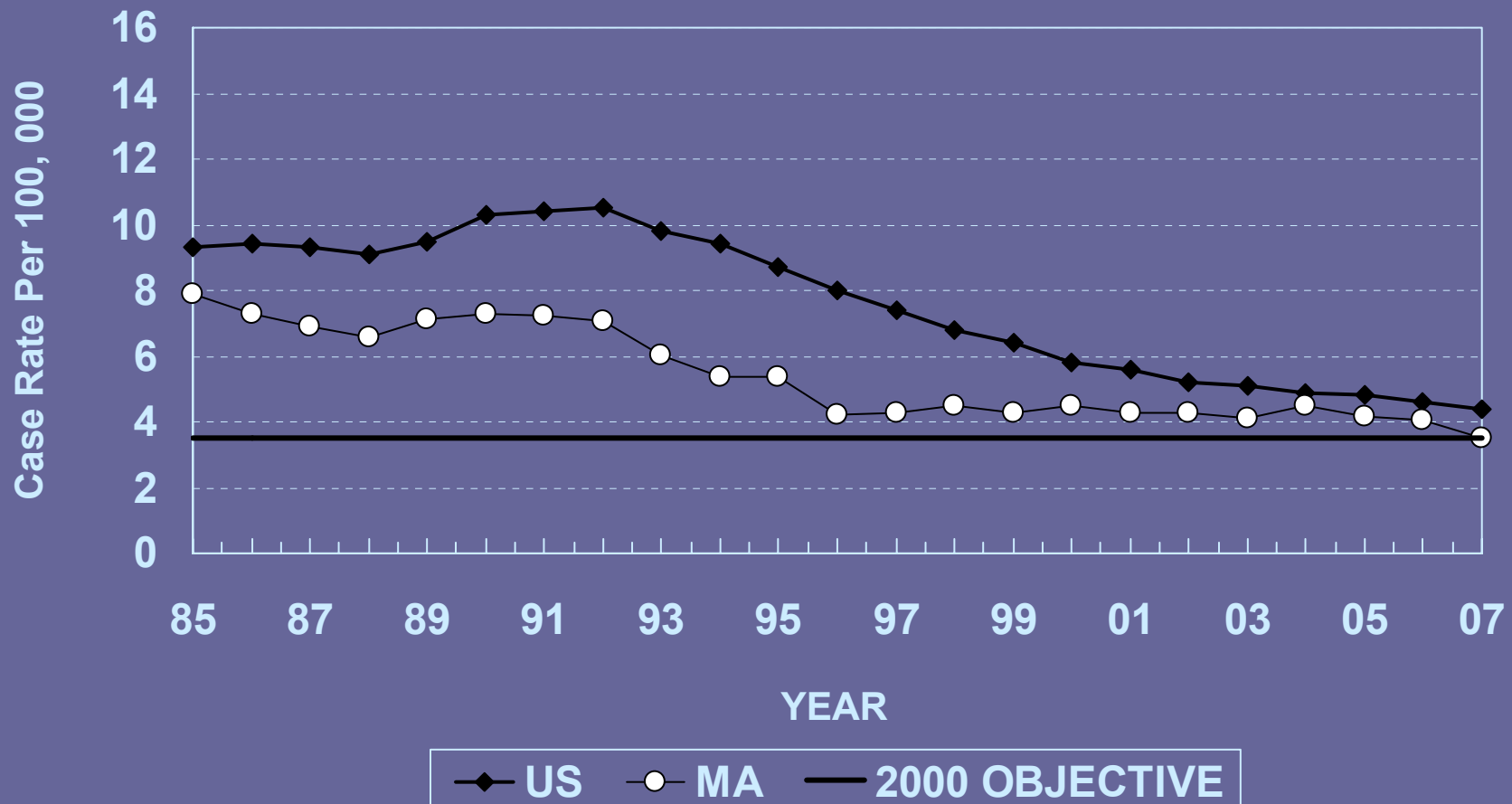
MDR/XDR

Fluoroquinolone Resistance

QuantiFERON and Treatment of LTBI

Moxi, Rifapentine, and the Universe

# United States and Massachusetts Tuberculosis Case Rates, 1985-2007



2007 US: 13,293 cases (4.4/100,000)  
4% *decr.* vs 2006  
MA: 224 cases (3.5/100,000)  
13% *decr.* vs 2006

# Trends in TB, 2007

- Rate of decline is slowing
  - 7.3%/yr 1993-2000; 3.8%/yr 2000-2006
- Increasing proportion of non-US-born
  - 21.9/100,000 pop (9.5 × rate of US-born)
- Blacks, Asians, and Hispanics
  - 8.4, 21.2, and 7.6 × rate among Whites
- Impact of HIV
  - 12.4% of cases (*with known status*)
- MDR
  - Appr. 1.2% of cases (124 cases in 2005)

# Pressing On ...



# *Extensively Drug Resistant (XDR) Tuberculosis*

- *Defined* (WHO, 10/10/06): Resistance to INH + Rifampin (MDR), *plus* any fluoroquinolone and at least 1 of 3 injectable second-line drugs
  - Capreomycin, kanamycin, amikacin
- Worldwide: 20% MDR, 2% XDR (est.)\*
  - Latvia: 19% (115/605) of MDR cases XDR (2000 – 2002)
  - South Korea: 15% of MDR cases XDR (2000 – 2002)
- Increasing XDR/MDR in E. Europe, Africa
  - KwaZulu-Natal, 2006: 544 Cult + / 221 MDR / 53 XDR / 52 died
- In US (2000 - 2006)
  - XDR/MDR::17/381 (4.5%)
  - Reported in NY/NYC, NJ, RI
- XDR *versus* MDR
  - More likely to die or experience treatment failure
  - At least 2/17 (12%) US cases died during tx (10 unknown outcomes, at time of report)
  - 1 famous case ... or what?

\* CDC:MMWR 56(11): 250-253, 3/23/2007

# *Extensively Drug Resistant (XDR) Tuberculosis.*

## *What now?*

- Not much new!
  - Still associated with high mortality
- Standardization of 2<sup>nd</sup>-line DST
  - CDC panel, Atlanta, 12/07
    - Developing program of work
  - Some issues
    - Standardizing buffers; solvents
    - Critical concentrations vs MIC's
    - Costs
    - Expertise
    - ?Regionalization of lab services
  - WHO panel, Geneva, 7/07
    - Policy, technical guidance, QC

# IDSA / ATS: *Empirical Antibiotics for Community Acquired Pneumonia and FQN's*

## ■ Outpatient

- 1. Previously healthy and no use of antimicrobials within the previous 3 months
  - A macrolide (strong recommendation; level I evidence)
  - Doxycycline (weak recommendation; level III evidence)
- 2. Presence of comorbidities such as chronic heart, lung, liver or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; or use of antimicrobials within the previous 3 months (in which case an alternative from a different class should be selected)
  - A **respiratory fluoroquinolone** (moxifloxacin, gemifloxacin, or levofloxacin [750 mg]) (strong recommendation; level I evidence)
  - A b-lactam **plus** a macrolide (strong recommendation; level I evidence)

## ■ Inpatients, non-ICU

- A **respiratory fluoroquinolone** (strong recommendation; level I evidence)

## ■ Inpatients, ICU

- b-lactam + azithromycin or **respiratory fluoroquinolone**

## ■ Our Letter: **When do we NOT use FQN??**

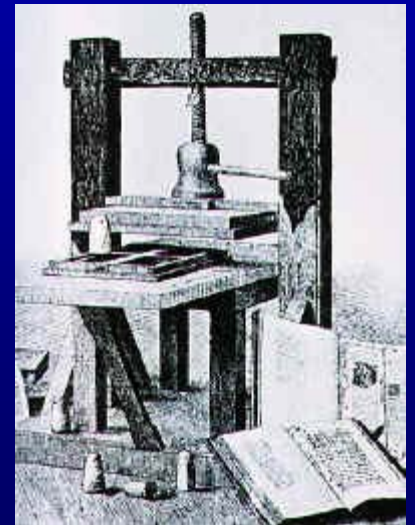


# Responses to *The Letter*

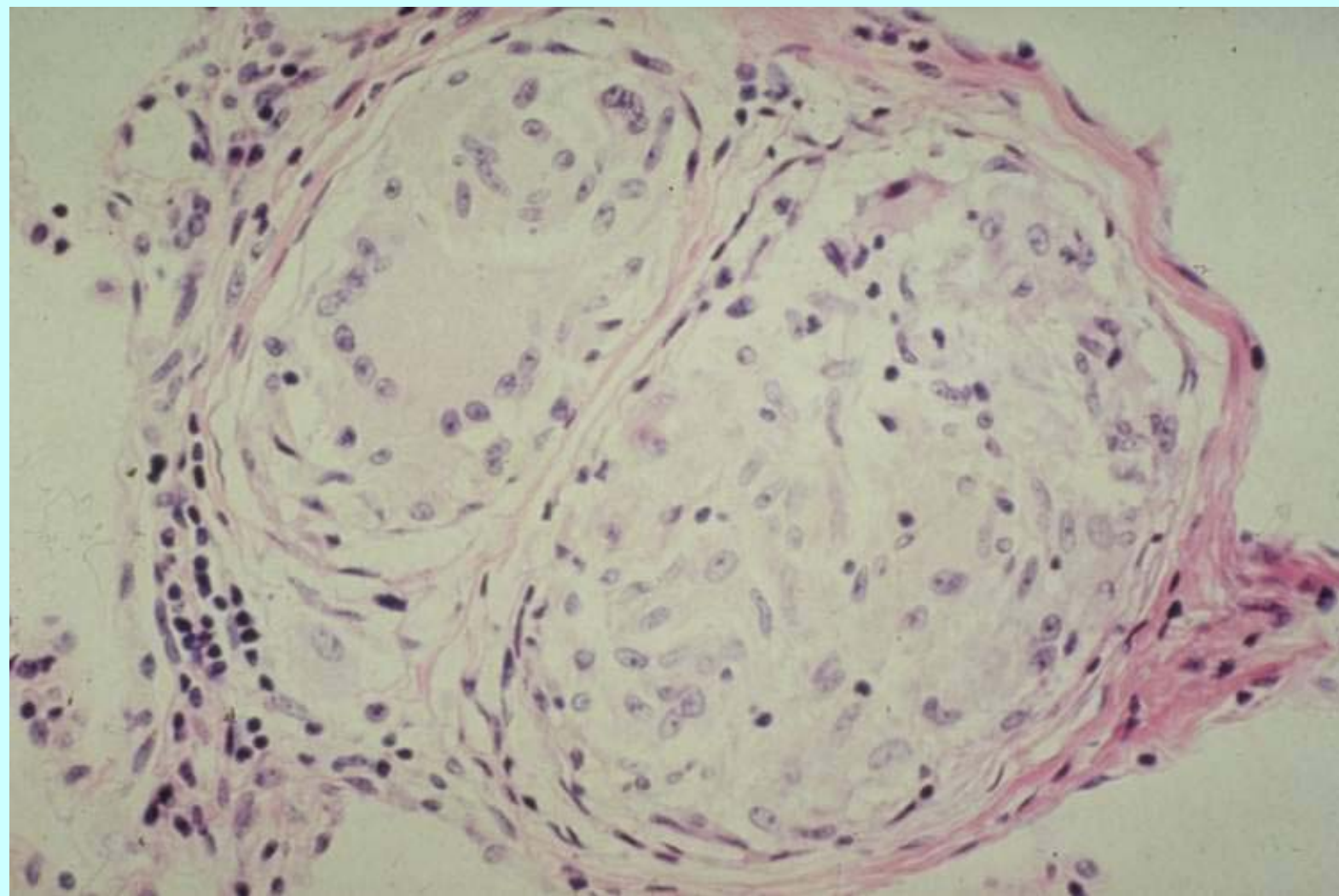
- IDSA (+/- ATS): *Thank you, but we will take care of it next time ...*
- ACET: *Acknowledges the issue; will advise CDC, support MMWR article*
- CDC: OK. Case-Based MMWR article *in-preparation*
  - *Inappropriate use of FQN's in unrecognized pulmonary TB: Prolonged transmission, 2° FQN resistance*



Johannes Gutenberg

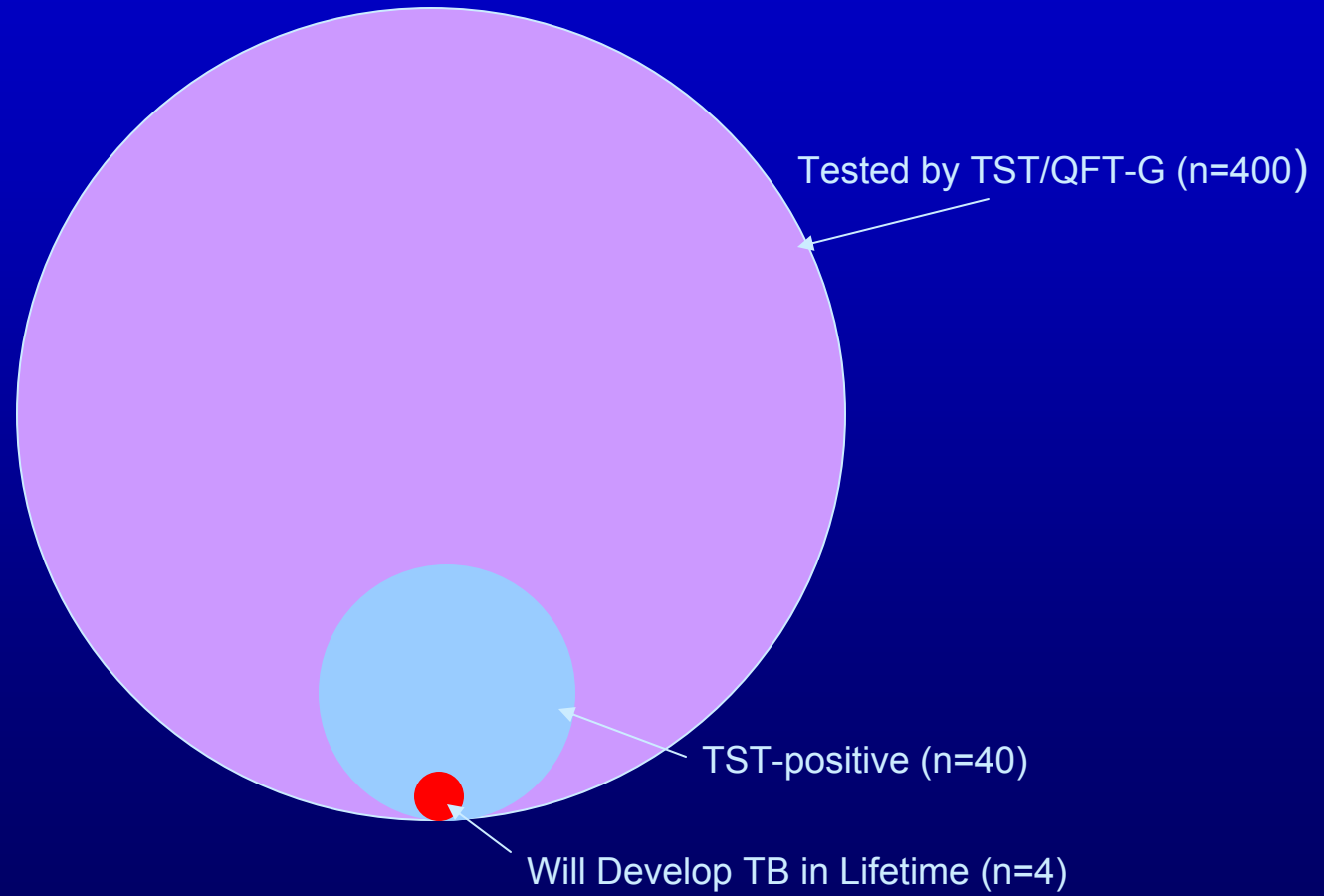


Mainz, Germany  
1436



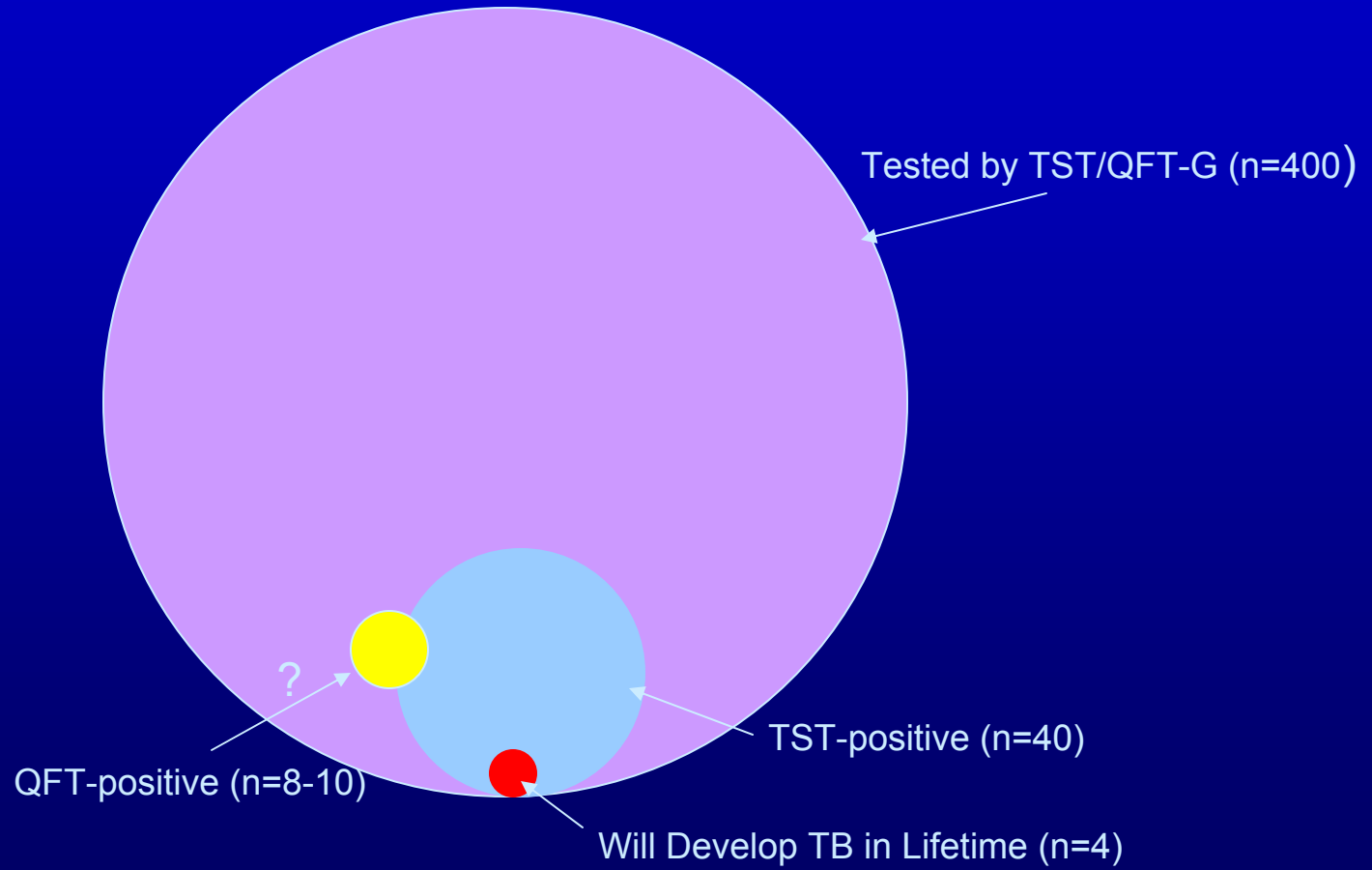
# QFT-G 2006

## Sensitivity for LTBI?



# QFT-G 2006

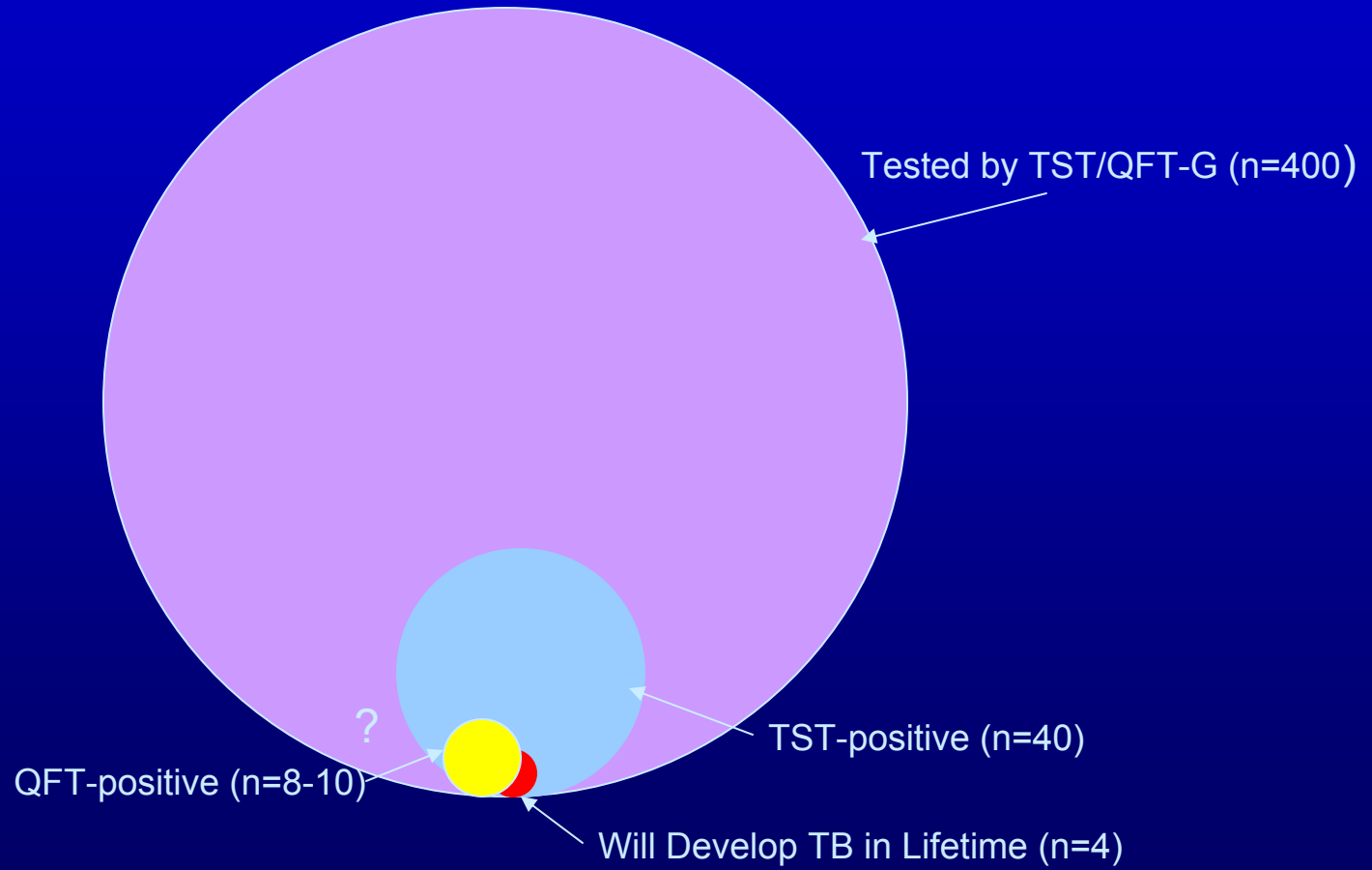
## Sensitivity for LTBI?



*or ...*

# QFT-G 2006

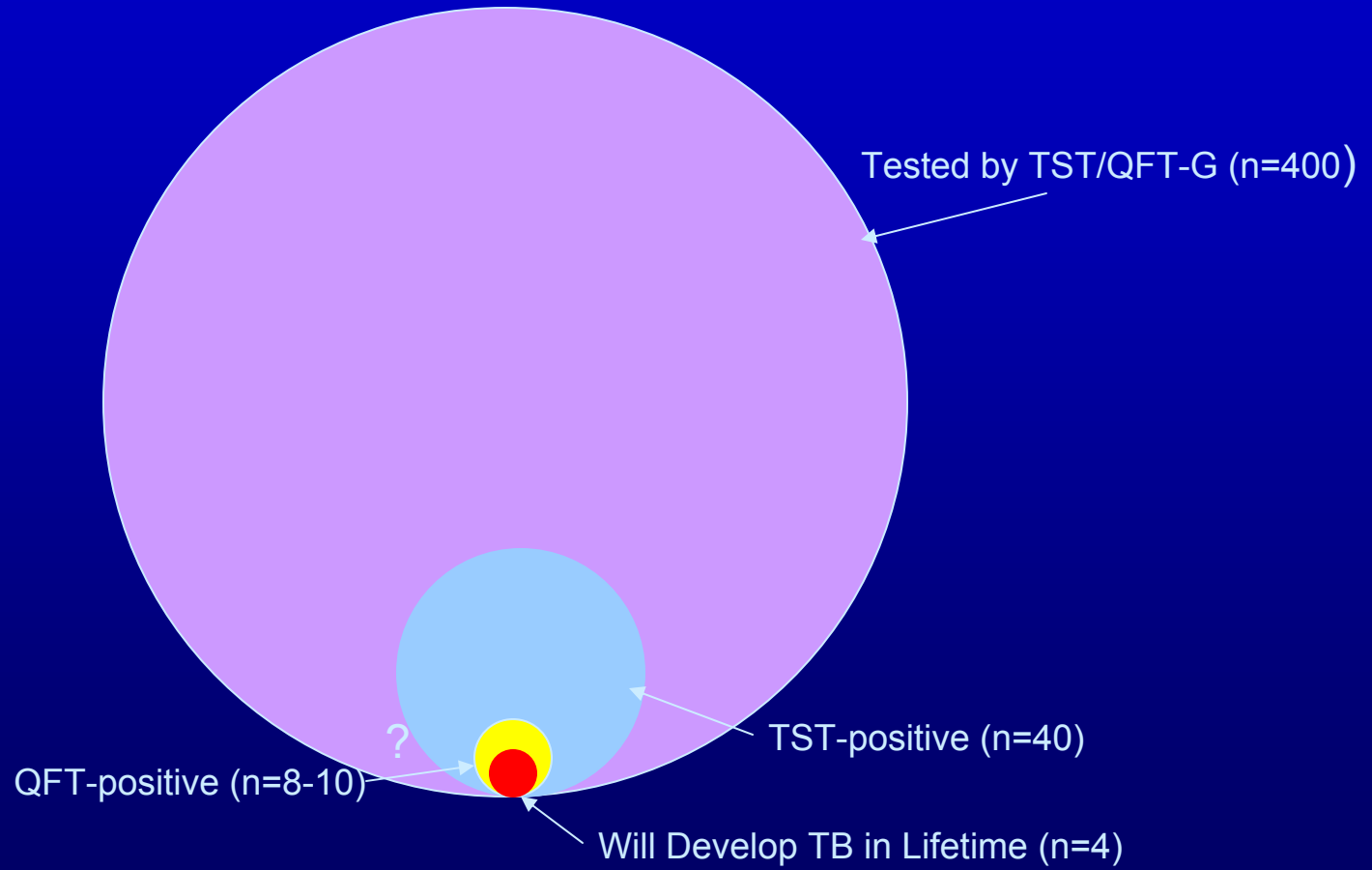
## Sensitivity for LTBI?



*or ...*

# QFT-G 2006

## Sensitivity for LTBI?



# *The Answer?*

## ■ TBTC Study 19

- Study of QFT-G-IT in *household contacts*
  - To follow QFT-neg contacts for 1 yr
  - To assess acceptance of QFT result by contacts, *re.* perception of need for treatment
- 2 national sites
  - SF, Chicago

## ■ Diel, *et al.* \*

- 601 household contacts x 103 wk
  - 243 (40%) TST+; 66 (11%) QFT-pos
  - 6 developed TB; *all were QFT-pos, declined tx*
- *BUT:*
  - *no indeterminates (in 292 tested w mitogen)*
  - *Small numbers*





©1997 Laura Coldwell

# Treating LTBI: *TBTC Study 26*

- Randomized, open-label Phase III clinical trial of short-course treatment of high-risk LTBI
  - 3-month, once-weekly regimen of INH plus rifapentine (12 doses, DOT), *versus*
  - 9-month therapy with INH (270 doses, self-administered)
- Contacts, TST converters, HIV-pos, abnl CXR
- Adults and children
  - $\geq 2$  y/o
- Safety *and* effectiveness: *2 yr follow-up*
- Sub-studies: *Hepatotoxicity; Hypersensitivity; Pedi RPT-PK*
- 8,000 persons enrolled – NOW IN FOLLOW-UP
  - Continuing to enroll children (<5 y/o) and HIV+

# Treatment of Tuberculosis

## *What Is Needed ?*

- Shorter and simpler treatment
- Improved treatment of LTBI
- Treatment of children
- Stop generating “MDR” TB
- Treat TB & AIDS simultaneously



Saskatchewan Lung Association

# *Clinical Testing*

- Diarylquinoline TMC207, Johnson & Johnson
- Nitroimidazopyran PA-824, GATB
- Nitro-Dihydro-Imidazooxazole OPC-67683 Otsuka
- ~~Gatifloxacin OFLOTUB Consortium/WHO~~
- Moxifloxacin  
CDC TBTC & Bayer  
Johns Hopkins University  
NIAID TBRU  
TB Alliance
- Pyrrole LL-3858, Lupin Limited
- Rifamycins??

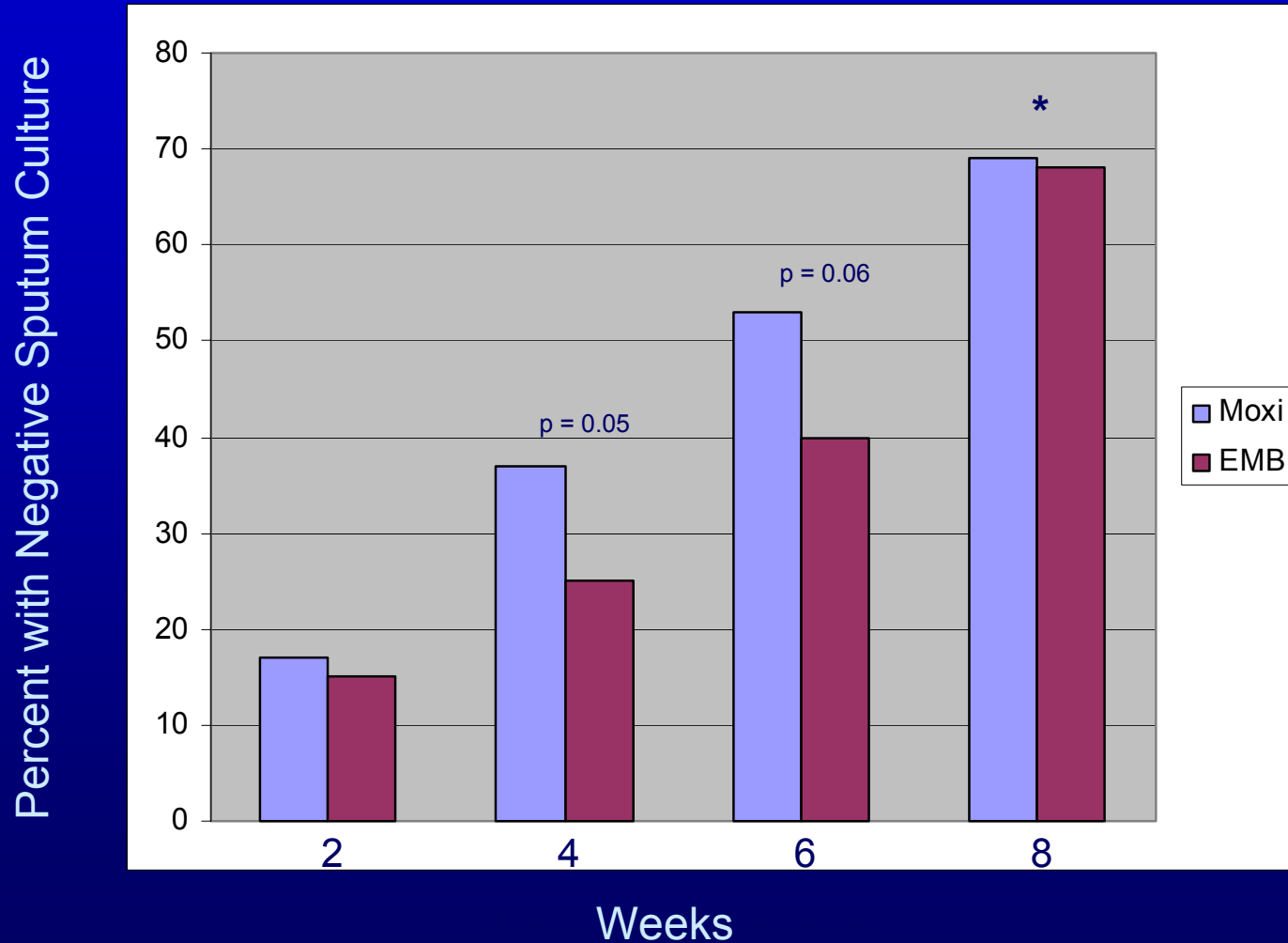
# TBTC Study 27

- Phase II trial of Moxi substituted for EMB in standard intensive-phase therapy
  - Smear-positive sputum
- US and African sites
  - n = 277 subjects (~37% N Amer/63% African enrollment)
  - Appr. 51% with cavitation
- End point: Sputum culture conversion at 2 months

PRELIMINARY

# TBTC Study 27

## Sputum Culture Conversion



\* But 87/102 (85%) N. American vs 110/175 (63%) African  
Cult neg at 8 wk. ( $p < 0.0001$ )

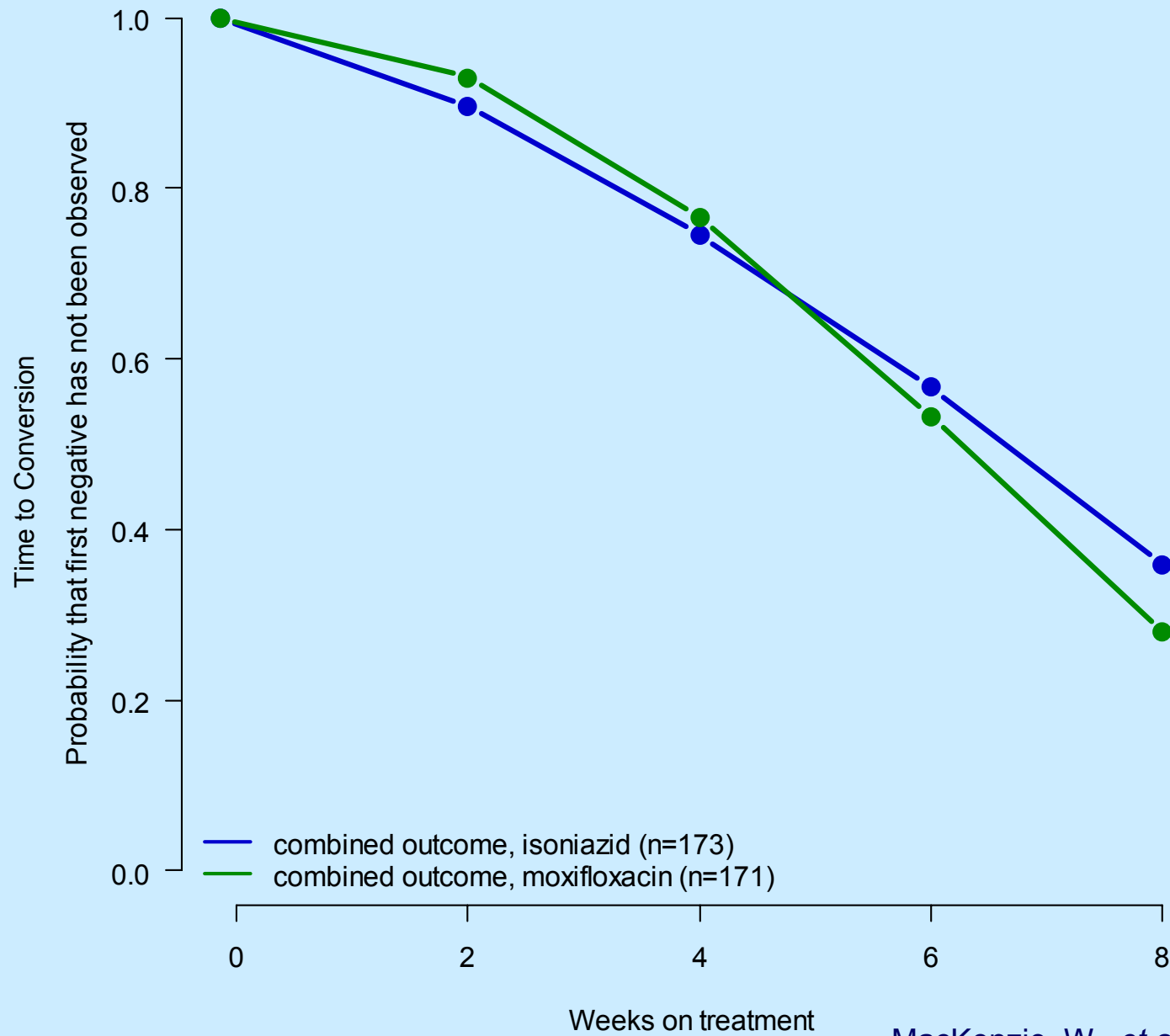
# TBTC Study 28

- Phase II trial of Moxi substituted for INH in standard intensive-phase therapy
  - Smear-positive sputum
- US and African sites
  - n = 344 subjects (~36% N Amer/64% African enrollment)
  - Appr. 27% with cavitation
- End point: Sputum culture conversion at 2 months

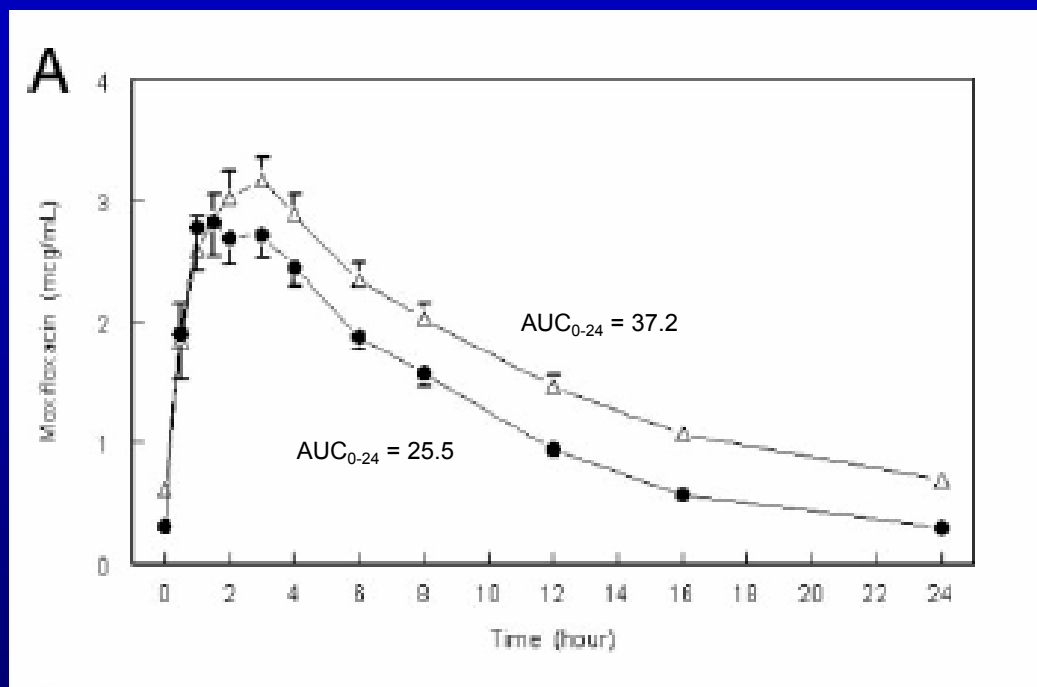


PRELIMINARY

# TBTC Study 28



# Mean Plasma Moxifloxacin, with/without Rifampin in Volunteers



△ Moxi (400mg/d) x 4d

● Moxi (400mg/d) + Rif (600mg/d) x 10d

Weiner, *et al*, Antimicrob Agents Chemother,  
51:2861-6, 2007

# Rif at >10mg/kg/d???

- Rifampin at 10 mg/kg
  - Used for decades for TB treatment
  - However, evidence using animal models has suggested that higher doses of rifampin are likely to be more active. (e.g. Verbist, L., 1969)
- Rifampin at >10 mg/kg?
  - Information from clinical trials *and experience* suggests that rifampin doses >10 mg/kg may be well-tolerated when rifampin is given daily
    - no significant difference in the incidence of adverse events between the 450 mg, 600 mg and 750 mg rifampin treatment arms in the USPHS trial (Long, *et al*, 1979).

# Rifapentine (RPT)

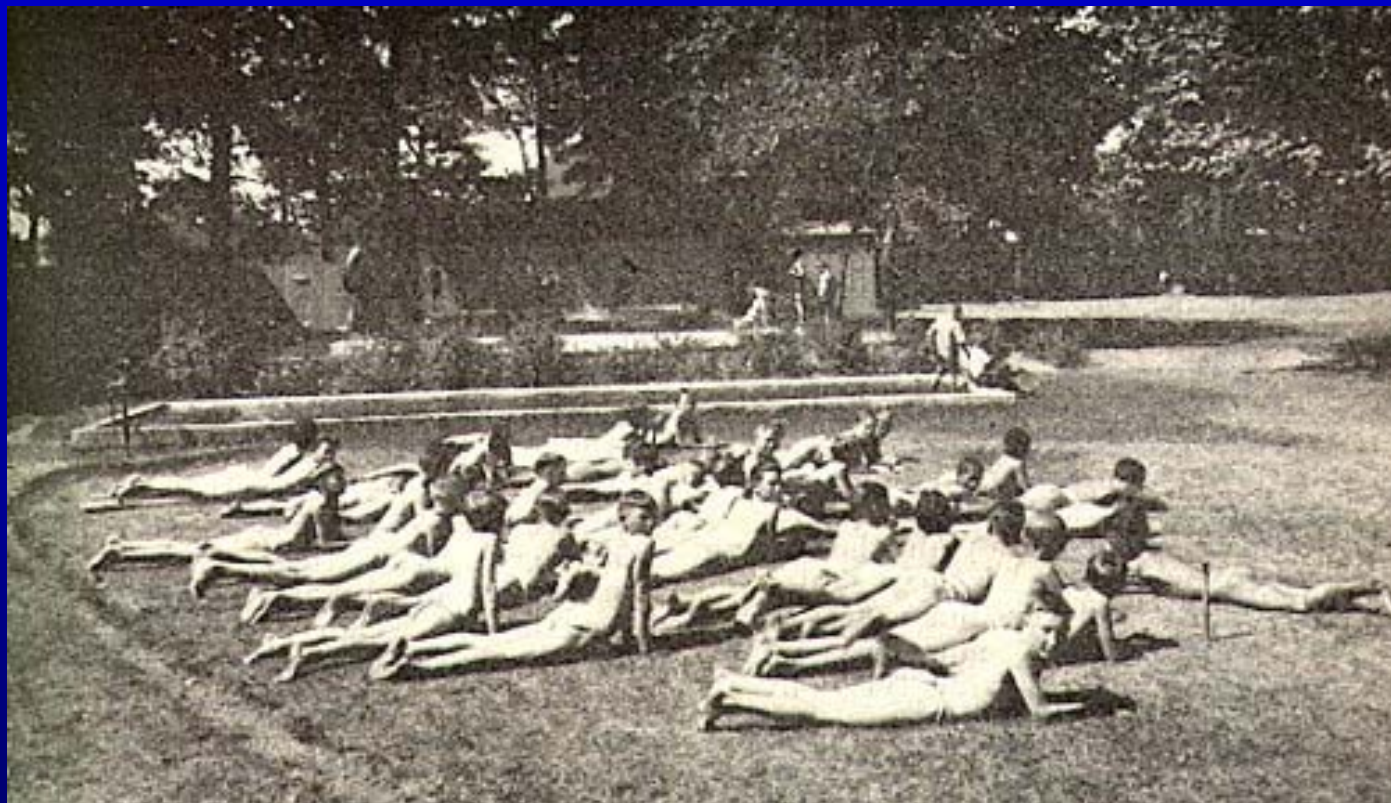
- MIC<sub>50</sub> and MIC<sub>90</sub> are 1- to 2x dilutions lower than those of rifampin
  - In 7H10 agar, RPT's MIC<sub>50</sub> and MIC<sub>90</sub> are 0.125 and 0.25, vs 0.5 and 1.0 for rifampin (Bemer-Melchior, *et al.*, 2000).
  - t<sub>1/2</sub> is 5x longer than that of rifampin
    - 14-18hr vs. 2-5 hr
- Attractive candidate for intermittent treatment regimens. (McDonald, *et al.* 1982; Cohn, *et al.* 1990)
- **Increased rifamycin exposure can be achieved either by using rifampin at doses higher than 10 mg/kg, or by using RPT**

# ***Evaluation of a rifapentine-containing regimen for intensive phase treatment of pulmonary tuberculosis. TBTC Study 29***

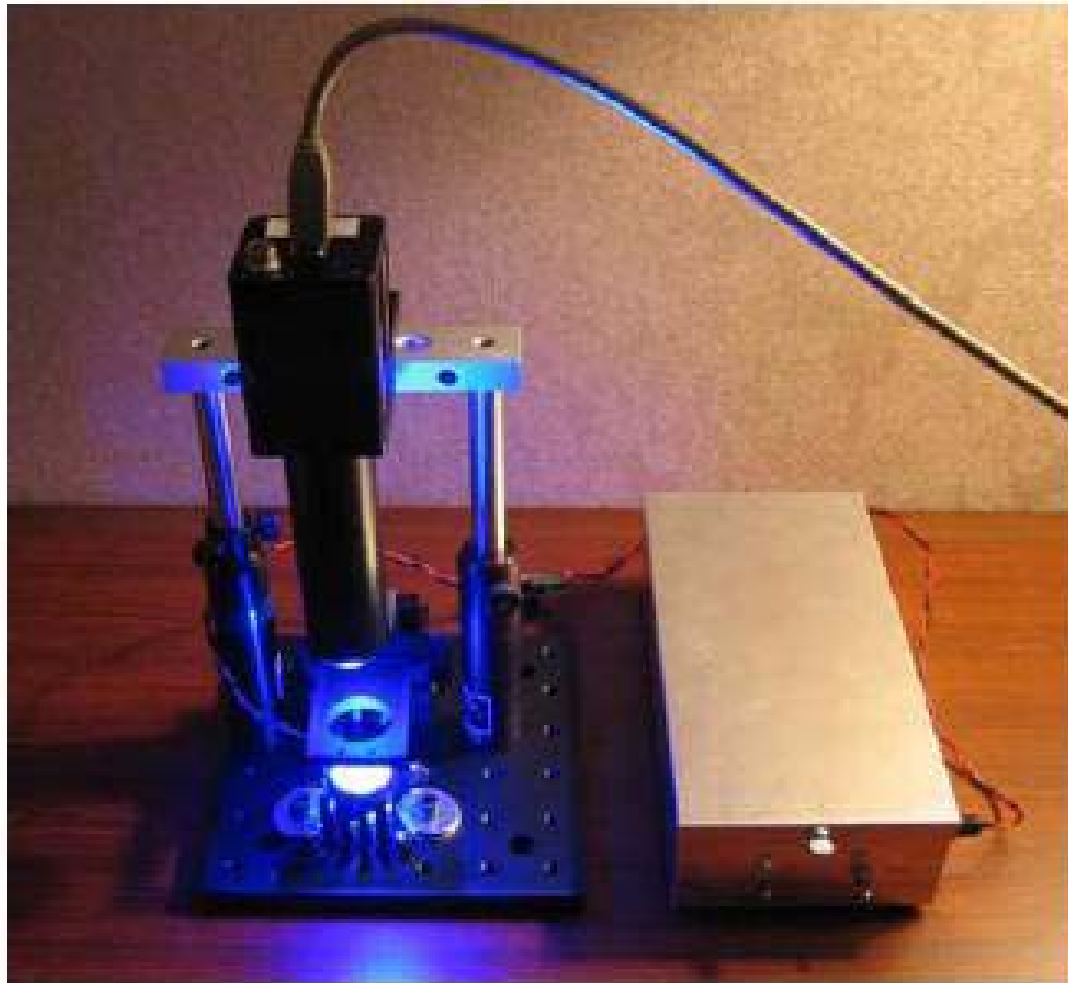
- Study of **antimicrobial activity** and **safety** of a standard daily (5/7d) regimen: ***rifampin*** (appr 10 mg/kg/dose) + INH + PZA + EMB (RHZE) ***versus*** an experimental regimen: ***rifapentine*** (appr 10 mg/kg/dose) + INH + PZA + EMB (PHZE) in sputum smear-positive pulmonary tuberculosis
- Two month sputum culture conversion/biomarkers
- Standardized laboratory parameters

# *Shorter and Simpler?*

- *We have progressed from 24\* to 6 months*
- Finally! New drugs in the pipeline:
  - demonstrate greater activity vs MTb
  - driven by unique mechanisms of action
  - offer potential for weekly dosing
- Long-term Vision:
  - $\leq$  2 month course of treatment !(?)



Heliotherapy (sun therapy)  
*Valley Echo*, April, 1927



**Figure 2. A minimalist image cytometer.**





Figure 3. Image cytometer pictures of positive and negative sputum slides stained with the low-background fast auramine O stain (Scientific Device Laboratory).

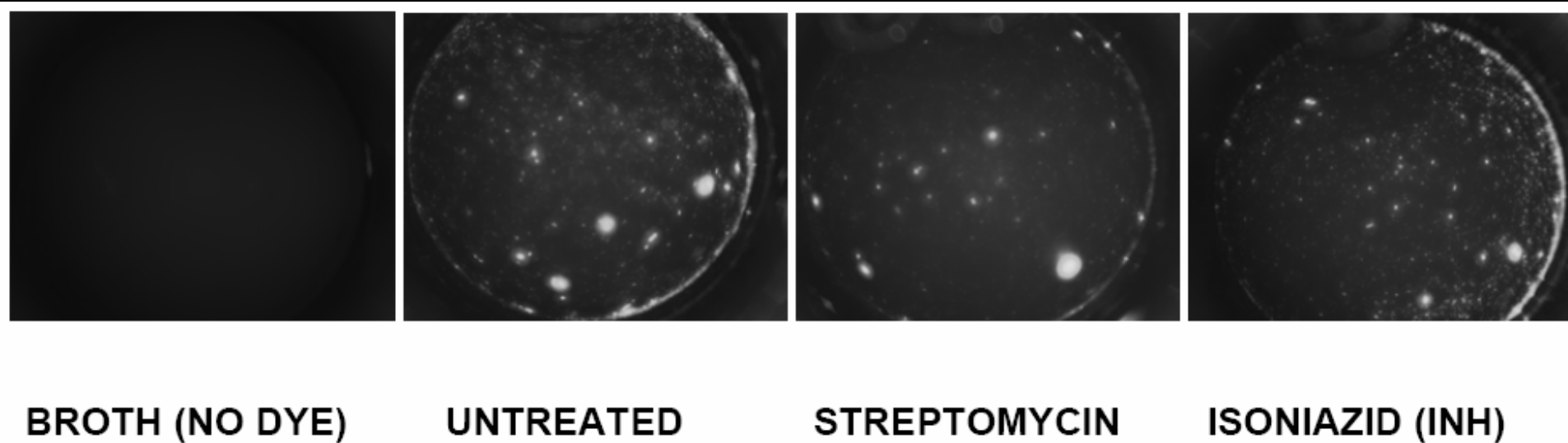
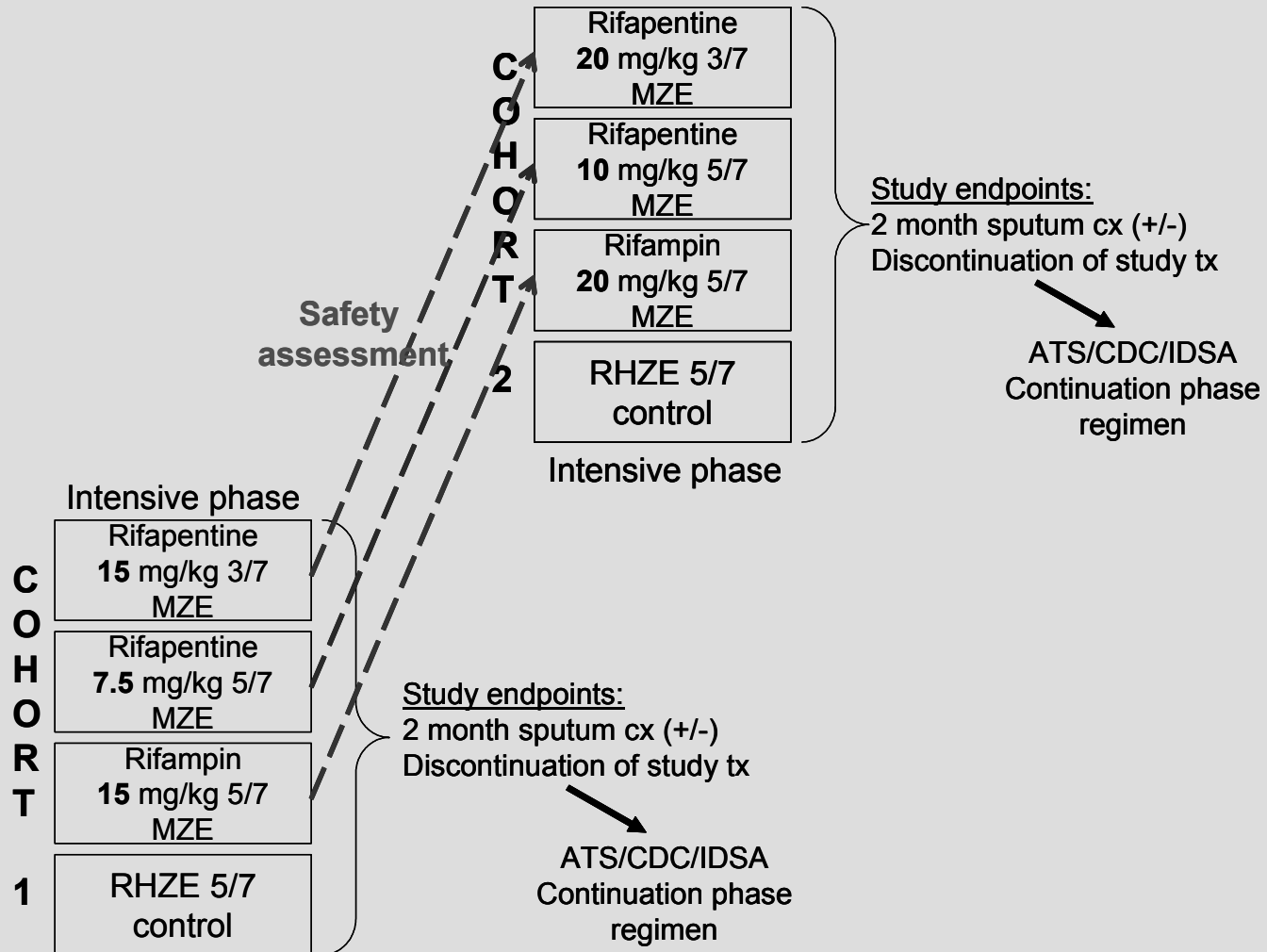


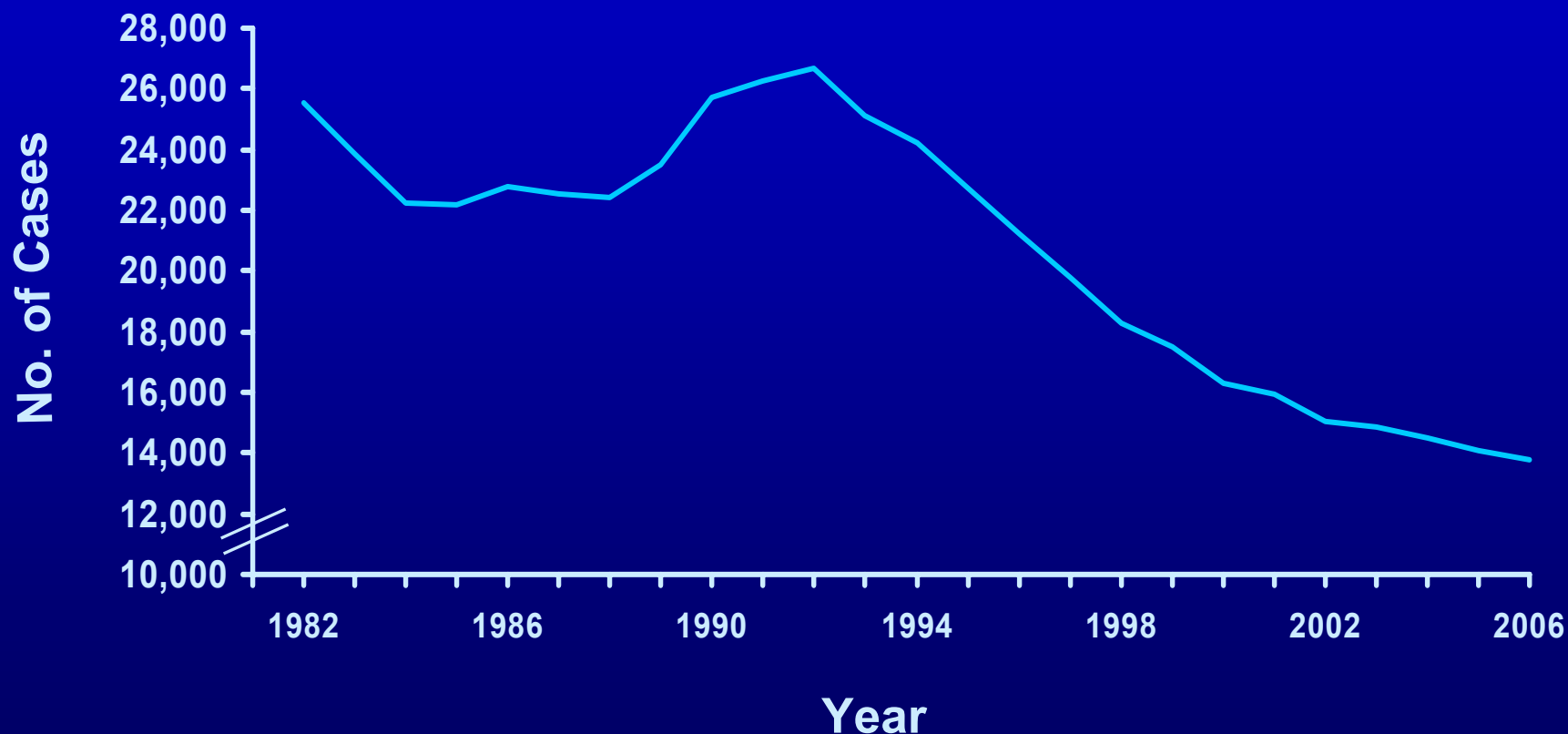
Figure 4. *M. smegmatis* drug susceptibility by image cytometry.

# Evaluation of moxifloxacin-containing regimens with increased rifamycin exposure for treatment of pulmonary tuberculosis *TBTC Study 29*



# Reported TB Cases\*

## United States, 1982–2006



\*CDC

2006: 13,767 cases (4.6/100,000)  
3% *decr.* vs 2005